

**Evaluation of Serial Beta-human Chorionic  
Gonadotrophin Levels after Primary Treatment of  
Molar Pregnancies.**

**Can the Follow-Up for Surveillance of Persistence or  
Malignant Transformation be shortened?**

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## **“Declaration**

I, the undersigned, hereby declare that the work contained in this assignment is my original work and that I have not previously submitted it, in its entirety or in part, at any other university for a degree.

**Signature:** .....

**Date:** ..... “

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## **Abstract**

**Objective:** *The aim of the study was to determine whether Beta-hCG levels at various time intervals during the follow-up period after primary treatment of molar pregnancies could be used to predict progression of the disease later, in an attempt to shorten the period of surveillance. Furthermore an assessment of the demographic details and risk factors for the development of persistent trophoblastic disease was examined. Levels of compliance to the current surveillance protocol were evaluated.*

**Method:** *A retrospective analysis of all patients diagnosed with molar pregnancies at Tygerberg Hospital, Cape Town from January 2000 to December 2010.*

**Results:** *Among the 120 patients, 13 (19.7%) of complete moles and 10 (20%) of partial moles developed persistent trophoblastic disease. There was no statistical significance of the demographic data when comparing the two types of moles. 66% of complete and 50% of partial moles were lost to follow-up within the first six months of surveillance. A potential Beta-hCG cut-off value of 148mIU/ml at week 6 offered a sensitivity of 0.89 and specificity of 0.88 that surveillance could be terminated.*

**Conclusions:** *Patient compliance is a limiting factor in the evaluation of molar pregnancy surveillance. However, based on our results, the suggestion that termination of surveillance after primary evacuation could occur at 6 weeks if the Beta-hCG level was 148 mIU/ml or lower remains undecided, and it is our opinion that higher sensitivities and specificities are required. Further research is needed to solidify this claim. The acquisition of demographic information of our population remains a priority, in order for more informed decisions to be made.*

## **Abstrak**

**Doel:** Die doel van die studie was om te bepaal of Beta-mCG vlakke of verskillende intervale, gedurende die opvolg periode na primêre behandeling van mola swangerskappe gebruik kan word om siekte progressie te voorspel, en sodoende die tydperk van opvolg te verminder. Verder was die demografiese besonderhede en risiko faktore vir die ontwikkeling van persisterende trofoblastiese siekte ondersoek. Die nakoming tot die huidige toesighouding protokol was geëvalueer.

**Metode:** 'n Retrospektiewe analise van al die pasiënte wat gediagnoseer is met 'n mola swangerskap by Tygerberg Hospitaal, Kaapstad vanaf Januarie 2000 tot Desember 2010.

**Resultate:** Van die 120 pasiënte het 13 (19.7%) van die volledige molas en 10 (20%) van die gedeeltelike molas persisterende trofoblastiese siekte ontwikkel. Daar was geen statistiese belang in die demografiese data, wanneer die twee tipe molas met mekaar vergelyk is nie. 66% van die volledige en 50% van die gedeeltelike molas was verlore met opvolg binne die eerste ses maande van opvolg. 'n Potensiële Beta-mCG afsnywaarde van 148mIU/ml op ses weke het 'n sensitiviteit van 0.89 en spesifisiteit van 0.88 gewys dat toesighouding getermineer kan word.

**Opsomming:** Pasiënt nakoming is 'n beperkende faktor in die opvolg van mola swangerskappe. Alhoewel, gebaseer op ons resultate, ons kan voorstel dat terminasie van "surveillance/toesighouding" na primêre lediging, kan plaasvind op 6 weke indien die Beta-mCG vlak 148mIU/ml of minder is, bly dit onbeslis. Dit is ons opinie dat hoër vlakke van sensitiviteit en spesifisiteit nodig is. Verdere navorsing is nodig om hierdie voorstelling te staaf. Die invordering van demografiese inligting van ons populasie bly 'n prioriteit, om sodoende meer ingeligte besluite te neem.

## **Introduction and Literature Review**

Gestational trophoblastic disease (GTD) defines a heterogeneous group of interrelated lesions arising from the epithelium of the placenta. Hydatidiform molar (HM) pregnancy is the most common form of GTD; this includes both partial hydatidiform molar (PHM) and complete hydatidiform molar (CHM) pregnancies <sup>[1]</sup>. The pathogenesis of GTD is unique because the maternal tumour arises from gestational rather than maternal tissue. All these conditions exhibit proliferation of both cytotrophoblast and syncytiotrophoblast cells. Complete (CHM) and partial moles (PHM) are non-invasive, localized tumours that develop as a result of an aberrant fertilization event that leads to a proliferative process.

At the 2000 International Federation of Obstetrics and Gynecology (FIGO) meeting, the term 'gestational trophoblastic neoplasia' (GTN) was recommended for patients whose serum beta-human chorionic gonadotrophin (Beta-hCG) level failed to regress in the absence of a normal pregnancy. These patients, similar to those with choriocarcinoma, need chemotherapeutic treatment.

The incidence of GTD varies widely in different regions of the world <sup>[2]</sup>. The incidence of hydatidiform mole ranges from 23 to 1299 cases per 100,000 pregnancies, while GTN is less common. North American and European countries tend to report low or intermediate rates of disease, whereas Asian and Latin American nations often have high rates. The incidences, reported in literature, from Europe and North America are quoted as 0.5 to 1 per 1000 pregnancies per year, whereas those reported from South East Asia, Indonesia, India and Turkey are as high as 2 to 12 per 1000 pregnancies per year.

One reason for this variation is that epidemiologic data on GTD are limited by the rarity of the disease and inaccurate ascertainment of the number of cases as a function of the number of gestational events in the population, including normal pregnancies, ectopic pregnancies and miscarriages. Another reason for the differences in incidence worldwide is the discrepancy between population and hospital-based data. Due to the explanation mentioned above, the difficulty in estimating the true number of gestational events in a given population often necessitates the calculation of incidence based on the number of pregnancies recorded by a single institution. Very few countries worldwide have registries

whereby all molar pregnancies are recorded, this is especially true for under-developed countries.

There is no accurately recorded data for the incidence of molar pregnancies in South Africa. One study reported the incidence of molar pregnancies in Kwazulu-Natal, South Africa to be 1.16 per 1000 pregnancies. Whether this holds true for the Western Cape population and the rest of South Africa is not certain.

The two main risk factors for GTD are extremes of maternal age (especially over age 35 years) and a history of previous GTD <sup>[3]</sup>. The most well established risk factor for GTD is maternal age. Compared to the risk of GTD in the general population of reproductive-age women, the risk is significantly increased in those older than age 35, and slightly increased in those under age 20<sup>[4]</sup>. Nevertheless, most cases of GTD occur in women under age 35 because of the greater number of pregnancies among younger women. It has been postulated that the ova of females of advanced age are more susceptible to abnormal fertilisations.

The presence of a previous molar pregnancy increases the risk of a second molar pregnancy (complete or partial) to 1-2 %. The risk of a third molar pregnancy rises to 15-20 % <sup>[5]</sup>. Studies from the United States have found that women with a history of one molar pregnancy (partial, complete, or persistent GTN) have an approximately 1 % chance of recurrence in subsequent pregnancies (compared to a 0.1 % incidence in the general population of the United States). The recurrence rate is much higher after two molar pregnancies (16 to 28 %) <sup>[6]</sup>.

Assisted reproductive technology has enhanced the fertility potential of older women, which may increase the proportion of cases in this age group. This is of concern because malignant sequelae occur more frequently in older patients <sup>[7]</sup>.



Other risk factors that have been associated with GTD include current smoking (>15 cigarettes per day), maternal blood type AB, A, or B, history of infertility, nulliparity, and use of oral contraceptives (although oral contraceptives do not increase the risk of developing post-molar trophoblastic neoplasia<sup>[8]</sup><sup>[9]</sup>). The mechanism for these associations has not been established and increased risk has not been demonstrated consistently.

Hydatidiform molar pregnancies constitute approximately 80 % of all cases of GTD. Molar pregnancies comprise both CHM and PHM. These two entities have different histopathologic and chromosomal features, and more importantly their potential for persistence and progression to metastasis vary considerably too. Studies in the United Kingdom have reported malignant change in 15 % of CHM's and 0.5-1 % of PHM's<sup>[10, 11]</sup>.

#### Genetics of molar pregnancy

Complete mole genetics — A complete mole most commonly has a 46,XX karyotype, with all chromosomes of paternal origin<sup>[12]</sup>. This results from fertilization of an "empty" egg (ie, absent or inactivated maternal chromosomes) by a haploid sperm that then duplicates (46,YY moles do not occur because this karyotype is lethal). A small number (3 to 13 %) of complete moles have a 46,XY chromosome complement; this is thought to occur when an empty ovum is fertilized by two sperm<sup>[12]</sup>. A few complete moles have a 46,XX karyotype but develop from fertilization of an empty ovum by two sperm. Because the nucleus is entirely paternal in origin, a complete mole is actually a paternal allograft in the mother. Aneuploidy can also occur.

Rarely, complete moles are biparental and are associated with an autosomal recessive condition predisposing to molar pregnancy. These patients often have recurrent hydatidiform moles. This defect is likely due to dysregulation of genomic imprinting, in some cases related to a mutation at the 1.1 MB region on chromosome 19q13.4. As an example, women with biparental complete mole have significant underexpression of p57(KIP2), which is the product of CDKN1C (an imprinted, maternally expressed gene). Compared with women with androgenic complete moles, women with biparental complete

moles have a very high risk of recurrence, and also an increased risk of persistent trophoblastic disease. In one series of 152 pregnancies among 37 women with familial recurrent mole, complete mole and partial moles occurred in 74 and 4 % of pregnancies, respectively. A normal pregnancy developed in only 5 %, the remainders were described as spontaneous abortions (17 %) <sup>[13]</sup>.

**Partial mole genetics** — Partial moles are pathologically and karyotypically distinct from complete moles. They are usually (about 90 %) triploid (69,XXX, 69,XXY, rarely 69,XYY) due to the fertilization of an ovum (one set of haploid maternal chromosomes) by two sperm (two sets of haploid paternal chromosomes). Flow cytometry studies have revealed a variety of other karyotypes in the remaining 10 %, although the true existence of nontriploid partial mole has been challenged <sup>[14]</sup>. The fetal or embryonic tissue that is present with a partial mole will most commonly have a triploid karyotype.

### Histology of molar pregnancy

Hydatidiform moles are characterized by a marked proliferation of villous trophoblast associated with hydropic swelling of the chorionic villi. A major difference between the two types of molar pregnancy is that complete moles typically do not contain foetal/embryonic tissue and partial moles do, although foetal/embryonic tissue may be present in complete moles <sup>[15]</sup>.

The chorionic villi of a complete mole are diffusely hydropic and surrounded by hyperplastic, often atypical, trophoblast (table 1). Foetal tissue is not typically present. A twin pregnancy may be complicated by GTD, with a combination of a normal conceptus and a mole (complete or partial) and viable foetus or two moles. With the advent of ultrasonography at earlier gestational ages, molar pregnancies are being detected increasingly early, often as early as eight or nine weeks of gestation. The histologic features so characteristic of traditional complete moles, large hydropic villi and extensive trophoblast hyperplasia, are not typically seen at these early stages of development.

There are, however, distinctive histologic features seen in these "early complete moles" (often defined as a complete mole identified before 10 weeks gestational age). These include a cellular, myxoid-like villous stroma; markedly irregular villous contours (referred to as "toes and knuckles"); karyorrhectic debris visible in the villous stroma; and atypical trophoblasts (both villous and extravillous). Trophoblastic proliferation is not as marked as in more mature moles <sup>[16]</sup>.

In contrast to complete mole, a partial mole often contains normal appearing chorionic villi and fetal tissue admixed with hydropic villi (Table 1). The hydropic changes are focal and less prominent with less trophoblastic hyperplasia and atypia. Marked scalloping of chorionic villi and trophoblastic stromal inclusions are also seen. Differentiation of a partial mole from a hydropic abortus may be problematic. However, hydropic abortuses usually have a spectrum of villous sizes versus the two populations of villi in partial moles. Also, abortuses will have attenuated trophoblast over the surface of the hydropic villi while partial moles show at least modest trophoblastic proliferation <sup>[16]</sup>.

### Biochemistry of molar pregnancy

Gestational trophoblastic diseases all share a common biochemical marker, human chorionic gonadotrophin (hCG). HCG is a glycopeptide hormone, produced by syncytial trophoblastic tissue. It consists of 2 subunits, polypeptide chains alpha and beta. The beta chain is unique to hCG, while the alpha chain is shared with LH, FSH and TSH. This hormone is used to detect normal and abnormal pregnancy states. HCG is easily measured quantitatively in both urine and blood, and hCG levels have been shown to correlate with the volume of trophoblastic tissue present. In normal pregnancy the hCG is intact and hyperglycosylated (hCG-H) during the first trimester of pregnancy. In an abnormal pregnancy or a cancer state of trophoblastic tissue, there exists many subtypes of Beta-hCG; namely free-Beta-hCG, Beta-core, nicked-free-Beta and c-terminal peptide. Due to this array of subtypes, it has become increasingly necessary to produce commercial assays that are able to detect all subtypes. These assays are expensive and not readily available worldwide and as such, the risk of false negative test results in cases of trophoblastic disease is

unfortunately high. False positive readings are also possible due to cross-reacting antibodies, but these antibodies do not cross into the urine and thus false positive results can be excluded by the use of a urine test for confirmation. Molar pregnancies usually present with HCG values that are markedly elevated, approximately 40% of patients have HCG exceeding 100 000 mIU/ml. The serum hCG concentration is always elevated in women with GTD and is usually higher than that observed with intrauterine or ectopic pregnancies of the same gestational age <sup>[17]</sup>.

The Beta-hCG molecules, abundantly produced with molar pregnancies, exhibit specificity for the TSH receptors and have the potential to cause thyrotoxicosis. A serum Beta-hCG of 50,000 mIU/ml is approximately equivalent to a TSH level of 35 IU/ml.

The reference range for TSH at our laboratory is 0.35 to 4.5 IU/ml. Levels below 0.35 IU/ml signify a significant increase in the potential for thyrotoxicosis and thyrotoxic storm. These complications arise as a result of the large amount of circulating HCG in the maternal blood.

Diminished levels of TSH associated with elevated  $T_4$  will support the diagnosis of thyrotoxicosis. Free  $T_4$  (unbound, active thyroid hormone) must be checked in all patients, as elevated thyroid-binding globulin, as seen in pregnancy, and variable levels of albumin will alter free  $T_4$  levels and thus change measures of bioactive hormone.

Frequently patients exhibit clinical signs of thyrotoxicosis including hyperthermia, supraventricular tachycardia (SVT), congestive heart failure, gastrointestinal (GI) symptoms, and confusion without the complete picture seen with Graves' disease <sup>[18]</sup>.

### Gestational trophoblastic neoplasia

Factors that have consistently been shown to be predictors of development of GTN after a complete mole are:

1. Beta-hCG level over 100,000 mIU/ml
2. Presence of large (>6 cm in diameter) theca lutein cysts
3. Significant uterine enlargement

These are all signs of marked trophoblastic proliferation <sup>[19]</sup>. Complete moles with factors associated with increased risk of persistent disease are considered high-risk complete moles. For partial moles, no clinical factors have been identified that are associated with increased risk of GTN.

### Surveillance

After the primary management of a suspected or histologically-confirmed molar pregnancy the surveillance period begins. This period involves the evaluation of serial Beta-hCG levels. This is done in order to detect the presence of persistence, recurrence or malignant transformation early so that the method of secondary treatment can be offered early and improve the chances of success.

The International Federation of Gynecologists and Obstetricians (FIGO) standardized Beta-hCG criteria for the diagnosis of post-molar gestational trophoblastic disease. Any of the following findings during the period of gonadotropin follow-up is suggestive of persistent GTD and warrants treatment <sup>[20]</sup>:

- A plateau in the serum Beta-hCG concentration for at least four values over three weeks.
- A serum Beta-hCG concentration that rises (by 10 % or greater) for three values or more over at least two consecutive weeks.
- Persistence of detectable serum Beta-hCG for more than six months after molar evacuation.
- Histologic confirmation of choriocarcinoma.

Prophylactic chemotherapy after molar evacuation is widely practiced in developing countries in which poor medical and social resources limit effective follow-up <sup>[19]</sup>. However, this practice, which may cause later chemoresistance, is controversial and lacks universal acceptance. This practice is not offered at Tygerberg hospital.

The reasons for the need for a surveillance protocol are as follows:

1. As previously mentioned these conditions carry the potential to develop persistence, recurrence or malignant transformation
2. Early diagnosis allows for early secondary intervention (chemotherapy) which has an almost 100 % cure rate
3. The prognosis worsens once detection of persistence is based on clinical rather than biochemical means.

Previously, the follow-up of molar pregnancies, with Beta-hCG levels was continued to a total time period of two years. The method by which this was done was as follows; weekly levels were examined until levels reached undetectable levels, thereafter levels were evaluated monthly for six months, then 3-monthly for six months, and finally six-monthly twice. Currently this approach has been reserved for those patients with GTN.

Traditional surveillance for post-evacuation development of persistence was as follows [21,22].

- Weekly Beta-hCG after evacuation until levels were below 5mIU/ml for 3 consecutive weeks
- Thereafter, monthly Beta-hCG tests for six months.
- Serum Beta-hCG is also suggested in patients with a previous molar pregnancy six weeks after a subsequent normal pregnancy.

This method of surveillance has numerous shortcomings. Petersen et al evaluated the impact on psychological symptoms, sexual function and quality of life. Feelings of depression and sadness have been attributed by patients to the diagnosis and failed pregnancy attempt to the involuntary delay in child-bearing as well as the need for constant surveillance. Grief was attributed to the loss of a potential child and feelings of uncertainty and confusion about their future reproductive potential. Fear of recurrence was also reported before and during subsequent pregnancies [23].

Another major concern with the traditional surveillance method is the cost impact on both patients and the institutions that provide the care. At Tygerberg, patients are required to pay a fee for each visit to the clinic where surveillance is undertaken. This is due to the fact that this surveillance is considered a tertiary service provided by the state and thus a fee is payable by the patient. Bearing in mind that the majority of these patients are from a socio-economically disadvantaged part of the population and that surveillance is only done at secondary and tertiary clinics, transport to these clinics is a financial burden for these patients. These factors have an effect on the compliance of these patients to the surveillance schedule which potentially has detrimental effects on their health.

Numerous recent studies have addressed the issue of this protracted period of surveillance following molar pregnancies. Wolfberg et al, displayed a progression to persistent GTN in 15 % of reported cases of CHM, and the rate of persistent GTN in those whose HCG levels fell spontaneously after evacuation, to undetectable levels was 0.2% <sup>[24]</sup>. This study recommended further investigation of this phenomenon in other reputable centres for validation of their findings with the intention of lowering the time period of follow-up for patients, especially those wishing to conceive. A follow up study by the same authors, showed that the risk of developing persistence after evacuation of CHM was 9 %, when Beta-hCG levels were below 200 mIU/ml in the fourth week or below 100 mIU/ml in the sixth week. Those patients with a Beta-hCG that declined to below 50 mIU/ml during their surveillance period were found to be at no more than 1.1% risk of developing persistent GTN. While levels above 2000 mIU/ml in the fourth week were associated with a 63.8 % risk of developing persistent GTN <sup>[25]</sup>. Another study from the Netherlands regarding CHM's, showed that 13.3 % of patients required chemotherapy for persistent disease and none of those patients whose hCG levels spontaneously fell to normal after evacuation developed persistent molar disease. It was concluded that for those patients whose levels fell to normal within 2 months of evacuation, surveillance could be discontinued <sup>[26]</sup>.

Lavie et al, attempted to determine the optimal duration of Beta-hCG surveillance after evacuation of PHM. The results supported the suggestion that a single undetectable Beta-hCG level after evacuation was sufficient follow up to ensure remission in patients with

partial moles. However, poor compliance (34 % of patients were lost to follow-up during the post-evacuation surveillance period) of patients proved problematic <sup>[27]</sup>. Wolfberg et al evaluated 284 women with PHM that completed their surveillance period and found that none of those that had spontaneous decline (238 patients) in serum Beta-hCG levels to undetectable levels developed subsequent persistent GTN <sup>[28]</sup>.

Wiesma et al, retrospectively analysed Beta-hCG levels in order to determine the risk of persistent GTN following PHM, and also aimed to review the present surveillance protocol being used. This study indicated that 1.7 % of all PHM patients needed treatment for malignant sequelae. In contrast, no patient diagnosed with PHM had a biochemical or clinical relapse after achieving undetectable levels of Beta-hCG, consistent with previous studies. The authors concluded that patients who have had a PHM could be followed by Beta-hCG weekly assays until normal levels are achieved and then follow-up could be safely discontinued <sup>[29]</sup>.

In 2007, a regional trophoblastic unit in the United Kingdom revised their surveillance protocol based on the evaluation of molar pregnancies in their database over a ten-year period. Previously, serum Beta-hCG measurements were taken every two weeks until the levels returned to normal. Thereafter, the surveillance period was based on the time taken for that level to be reached, before or after 56 days post-evacuation. Those patients that previously had levels return to normal after 56 days, were evaluated monthly for one year and then 3 monthly for a further year. In the study, 6 % of patients developed persistent disease and 98 % of these occurred within 6 months of evacuation. Thus the period of monitoring for uncomplicated cases, whose values returned to normal after 56 days, was decreased to six months <sup>[30]</sup>.

Kerkmeijer et al <sup>[31]</sup> reviewed all hydatidiform molar pregnancies in The Netherlands from 1995 to 2004. Of all those patients that spontaneously normalised after evacuation, only one developed recurrent disease. The majority of these patients were followed up for approximately 6 months.



## **Aim of the Study**

The primary objective of the study is to determine whether Beta-hCG levels at various time intervals during the surveillance period after primary treatment of molar pregnancies can be used to predict progression of the disease later. This is an attempt to shorten the period of surveillance.

The secondary objectives of the study are to evaluate the demographic details of patients affected by molar pregnancies in the Tygerberg Academic Hospital (TBH) drainage area of the Western Cape (Table 2).

An attempt to shorten the surveillance period before remission (the presence of three consecutive undetectable Beta-hCG levels) has been confirmed has not been undertaken previously. This approach is intended to take into account the high prevalence of non-compliance to protracted surveillance periods.

## **Methodology**

### **Data Collection**

This is a retrospective descriptive study. Data was collected of all cases of CHM's and PHM's treated and followed up by the Unit of Gynaecologic Oncology at Tygerberg Hospital between January 2000 and December 2010.

All molar pregnancies diagnosed at Tygerberg Hospital, or those diagnosed elsewhere but that received treatment at Tygerberg Hospital were used in this study. The cases were drawn from the unit of gynaecologic oncology and the department of anatomical pathology.

All files were collected from the medical records department and all data was recorded onto anonymous data sheets. The data was entered manually onto the data acquisition form and then transferred onto an Excel spreadsheet and analysed by a statistician from the Department of Biostatistics from the University of Stellenbosch statistician.

### Sample Size Calculation

The sample size was calculated to offer as much precision as possible in the calculation of the primary objective. For the purposes of this study the objective was to determine whether a Beta-hCG of  $< 5$  at 2 months after evacuation was sufficient to assume that persistent disease would not occur. Thus, for all patients the Beta-hCG at 2 months after evacuation (or the closest possible value) was recorded. In addition, based on follow-up data available, it was possible to determine whether progression or malignancy for any patient did actually occur. Using this information, the sensitivity and specificity of the proposed cut-off of  $<5$  could be evaluated, as well the positive predictive value and negative predictive value. Thus, the sample size was determined to offer the best possible precision in the estimation of the sensitivity and specificity in particular.

Based on past literature it was expected that approximately 15 % to 20 % of CHM's would ultimately result in progression or malignancy. Therefore, a sample size of 150 molar pregnancies would offer an estimated 15% precision in the estimation of the sensitivity, given the relatively small population of molar pregnancies.

### Analysis of Data

MS Excel was used to capture the data and STATISTICA version 9 (StatSoft Inc. (2009) STATISTICA (data analysis software system), [www.statsoft.com](http://www.statsoft.com).) was used to analyse the data.

#### Primary Objective:

As mentioned previously, the primary objective was to determine whether the Beta-hCG levels at 6 weeks, 2 months, 3 months or 4 months after primary treatment could be used to predict persistence or malignancy. The sensitivity and specificity of the proposed cut-off of a Beta-hCG of  $<5$  was evaluated, as well as the positive and negative predictive value. Therefore, the primary objective was that of sensitivity and specificity. If the proposed cut-off value at 2 months after evacuation was found to be both highly sensitive and highly specific then this could serve as motivation for a reduction of the follow-up period beyond 2 months after evacuation.

#### Analysis of Other Objectives:

Other authors have suggested various different cut-off values for prediction of molar pregnancies. These vary according to the cut-off value itself as well as the recommended time period at which to make the prediction. The former analysis involves the construction of a receiver-operating curve (ROC) to determine the best cut-off value that will result in the highest possible combination of sensitivity and specificity. The ROC analyses were repeated at different time points in order to develop a likely prediction rule in the Tygerberg population.

#### Descriptive Statistics:

Summary statistics were used to describe the variables. Distributions of variables were presented with histograms and frequency tables. Means were used as the measures of central location for ordinal and continuous responses and standard deviations as indicators of spread.

For any other analyses, the following general analysis rules applied:

Relationships between two continuous variables were analysed with regression analysis and the strength of the relationship measured with the Pearson correlation, or Spearman correlation, if the continuous variables were normally distributed. If one continuous response variable was to be related to several other continuous input variables, multiple regression analysis were used and the strength of the relationship measured with multiple correlation.

The relationships between continuous response variables and nominal input variables were analysed using appropriate analysis of variance (ANOVA). When ordinal response variables were compared versus a nominal input variable, non-parametric ANOVA methods will be used. For completely randomized designs the Mann-Whitney test was used.

The relation between two nominal variables was investigated with contingency tables and likelihood ratio chi-square tests.

A P-value of  $p < 0.05$  represented statistical significance in hypothesis testing and 95 % confidence intervals (CI) were used to describe the estimation of unknown parameters.

The study was approved by the local ethics committee. (Ethics number N11/02/030)

### **Results:**

One hundred and twenty patients with molar pregnancies were managed at Tygerberg Hospital between January 2000 and December 2010. These patients were:

- primarily diagnosed with a molar pregnancy and treated at Tygerberg Hospital, or
- diagnosed with a complicated molar pregnancy at a peripheral district hospital and transferred to Tygerberg Hospital for primary management, or
- managed at a peripheral hospital and during the surveillance period, found to have persistent disease requiring chemotherapy.

### **Demographic data**

Patient ages ranged from 13 to 51 years with a mean maternal age of 26.5 years (95% CI 24.9 to 28.2). The mean age for the PHM group was 26.4 years (95% CI 24.1 to 28.8) and 26.0 years (95% CI 23.7 to 28.4) for the CM group as represented by figure 2. There was no significant difference between the two groups, with a P-value of 0.633 (table 3).

Twenty-five patients were 35 years or older, and of these 8 (32%) developed persistent GTD. Ninety-five patients were younger than 35 years, and only 16 (16.8%) developed persistent GTD. There was no statistical significance between these two groups for the development of persistence, with a P-value of 0.057 (table 4).

The histological diagnosis was that of CHM in 66 cases (55%), PHM in 50 cases (42%) and unknown in 4 cases (3%), as no histological specimens were evaluated for the latter group.

The mean parity in this study population was 1.1 (95% CI 0.8 to 1.4). The mean parity for the PHM group was 1.2 (95% CI 0.8 to 1.7) and 0.9 (95% CI 0.5 to 1.4) for the CHM group as represented by figure 3. There was no significant difference between the two groups, with a P-value of 0.099 (table 3).

The mean gravidity in this study population was 2.2 (95% CI 1.9 to 2.5). The mean gravidity for the PHM group was 2.4 (95% CI 1.9 to 2.9) and 2.1 (95% CI 1.6 to 2.5) for the CHM group as represented by figure 4. There was no significant difference between the two groups, with a P-value of 0.094 (table 3). The number of primigravid females with CHM's and PHM's was 35 (58.3%) and 20 (40%) respectively.

The mean age of menarche in this study population was 13.71 (95% CI 13.47 to 13.98). The mean age at menarche for the PHM group was 13.84 (95% CI 13.41 to 14.27) and 13.62 (95% CI 13.30 to 13.94) for the CHM group as represented by figure 5. There was no significant difference between the two groups, with a P-value of 0.404 (table 3).

The mean age of the patients at their first pregnancy was 20.46 years (95% CI 19.7 to 21.21). The mean age at first pregnancy for the PHM group was 19.86 years (95% CI 18.97 to 20.75) and 20.58 years (95% CI 19.47 to 21.68) for the CHM group as represented by figure 6. There was no significant difference between the two groups, with a P-value of 0.445 (table 3).

Only 67 of the 120 patients had a serum TSH level evaluated on admission. The mean TSH value in this subgroup was 2.6 (95% CI -0.8 to 5.9). The mean TSH level for the PHM group (24 samples) was 0.8 (95% CI 0.2 to 1.3) and for the CHM group (43 samples) was 3.6 (95% CI -1.6 to 8.9) (figure 7). There was no significant difference between the two groups, with a P-value of 0.116 (table 3).

The mean initial Beta-hCG for the study population was 534415.5 (95% CI 368889.6 to 699941.3). The mean initial Beta-hCG for the PHM group was 625496.2 (95% CI 344874.4 to 906118.0) and for the CHM group 472715.6 (95% CI 265063 to 680367.7) (figure 8). There was no significant difference between the two groups, with a P-value of 0.855 (table 3).

Sixty two percent of patients with PHM's and 53% of the patients with CHM reported the use of nicotine (figure 9).

The most common method of primary treatment for molar pregnancies at Tygerberg Hospital was an evacuation of the uterus, either by suction curettage or sharp curettage. 98% of the patients were treated using a curettage technique. Other treatment modalities used were Total Abdominal Hysterectomy (TAH) and Salpingectomy (Figure 10). The salpingectomy was performed on a patient diagnosed with an ectopic pregnancy upon which a histological diagnosis of a CHM was made.

#### Evaluation of Beta-hCG Surveillance

Persistence of gestational trophoblastic disease was diagnosed on the basis of Beta-hCG levels gathered after primary treatment was performed. The diagnosis of persistence was made on the basis of the guidelines as set out by the International Federation of Gynaecologists and Obstetricians (FIGO) and described in the introduction.

Fifty-three of the 66 patients (80.3%) with CHM spontaneously developed undetectable Beta-hCG levels during surveillance after primary treatment. Forty of the 50 patients (80%) with PHM spontaneously developed undetectable Beta-hCG levels during surveillance after primary treatment. Thus, 19.7% (n=13) of patients with CHM and 20% (n=10) of patients with PHM developed persistence.

The age, parity, gravidity and initial Beta-hCG values of patients with persistent GTD did not differ significantly from those who did not develop persistent GTD. (Table 5).

The outcomes of the patients that presented for surveillance for the presence of persistent disease is shown in table 6.

Eighty percent of both CHM's and PHM's required no chemotherapy and went into spontaneous remission, while approximately 20% developed persistence during the surveillance period. All of the cases of persistence were diagnosed within the first 9 months of follow-up and appropriate measures were taken.

Sixty-six percent of CHM's and 50 percent of PHM's were lost to follow-up in the first 6 months after primary treatment.

Of the total number of molar pregnancies evaluated during this study, 74 % (CHM) and 60 % (PHM) did not follow up and never reached undetectable levels of Beta-hCG.

Eighty-six % (CHM) and 94 % (PHM) of molar pregnancies missed at least one visit during the first 6 months after primary treatment was performed.

Four Receiver Operator Characteristic (ROC) curves were created to compare Beta-hCG levels of partial and CHM's in an attempt to ascertain potential cut-off values at certain time intervals during the surveillance period at which follow-up could be safely terminated (table 7).

The intervals at which this potential cut-off value was evaluated were week 4, week 6, month 2 and month 3. Although numerous ROC curves were calculated, those mentioned above were determined to be the most suitable time intervals for evaluation based on current knowledge of GTD remission.

At Week 4, 83 cases were evaluated at this time interval. A Beta-hCG of 148 conveyed the best sensitivity and specificity to be considered a potential cut-off of surveillance (figure 11 and table 8).

At Week 6, 85 cases were evaluated at this time interval. A Beta-hCG of 148 conveyed the best sensitivity and specificity to be considered a potential cut-off of surveillance (figure 12 and table 8).

At Month 2, 86 cases were evaluated at this time interval. A Beta-hCG of 43 conveyed the best sensitivity and specificity to be considered a potential cut-off of surveillance (figure 13 and table 8).

At Month 3, 76 cases were evaluated at this time interval. A Beta-hCG of 11 conveyed the best sensitivity and specificity to be considered a potential cut-off of surveillance (figure 14 and table 8).

## **Discussion**

Tygerberg Hospital is a combined secondary and tertiary medical facility that serves a large portion of the Western Cape Province, comprising both urban and rural regions. Numerous molar pregnancies are thus managed by the other secondary level hospitals in the clinic and never present to Tygerberg if spontaneous remission after primary evacuation occurs.

In the index study the true incidence of molar pregnancies could not be established because the total number of conception events (denominator) and the total number of molar pregnancies (numerator) in the Tygerberg Hospital drainage area could not be ascertained

In the index study the calculation of the incidence of persistence was also not possible because the number of molar pregnancies in the entire Tygerberg drainage area could not be determined.

It is not feasible to send specimens for histological analysis of all miscarriages that occur in the region, thus a high index of suspicion based on ultrasound findings is an important screening tool which assists in the decision for further testing, either Beta-hCG or histological assessment of the conceptus after evacuation.

## **Demographic data**

### **Age**

Increasing age is the best-established risk factor for CHM with women over 40 years of age having a 5 to 10-fold higher risk than younger women<sup>[32]</sup>. Because of the higher number of



pregnancies in younger women, however, most complete moles occur in women under 35. However, maternal age has not been associated with risk of PHM. Numerous authors have shown an association between older maternal age and an increased risk of persistent disease<sup>[3,4]</sup>.

The index study did not show a significant difference in the ages of those that developed CHM or PHM. As expected, more molar pregnancies were diagnosed before the age of 35 years, in line with previous studies.

The odds ratio for having a molar pregnancy after the age of 35 years in the index study is 2.35. This is considerably lower than that reported by another author, namely 5.2, where age > 40 years was evaluated<sup>[33]</sup>.

The index study showed that women over the age of 35 years were somewhat more likely to develop persistent disease, although this did not reach statistical significance ( $P = 0.057$ ).

#### Parity and gravidity

There has been reported that nulliparous or females of low parity have an increased risk of developing molar pregnancies<sup>[33]</sup>. In the index study, primigravidae made up 58.3% and 40% of complete and PHM groups respectively. This is merely a descriptive analysis that correlates to previous findings.

#### Initial Beta-hCG

Furthermore, the index study was unable to corroborate previous reports of the importance of serum Beta-hCG at presentation, due to the statistical insignificance of the index study data<sup>[25]</sup>. Ayhan et al determined that pre-evacuation Beta-hCG levels above 100,000 mIU/mL have been found to predict persistent disease, but never with sufficient precision to guide management<sup>[34]</sup>. Niemann et al found that all their patients diagnosed with CHM's that presented with initial Beta-hCG levels less than 49 000 mIU/ml had spontaneous remission<sup>[35]</sup>. This level is extremely low and offers no assistance to the majority of patients, usually presenting with values in excess of 100 000 mIU/ml. The Beta-hCG levels at

presentation, in the index study, showed no statistical significance in predicting the development of persistence for either benign forms of molar pregnancy.

### Menarche

Other authors have reported that the risk of developing gestational trophoblastic neoplasia may also be linked to certain hormonal factors. This is based on the increased risk noticed in women with menarche after the age of 12, and the previous use of oral contraceptives. Our data did not support the association between menarche after age 12 and the increased risk of persistent disease <sup>[36]</sup>.

### TSH (Thyroid Stimulating Hormone)

In the index study, 24 cases of PHM had TSH levels recorded, of which 12 were less than 0.35 IU/ml (50%), while 43 cases of CHM had TSH levels recorded, of which 16 were less than 0.35 IU/ml (37%). Although these tests were requested, there is not much evidence to suggest that these values alerted the clinicians to any potential threat, and no notes were made on positive symptoms of thyroid crisis, thyrotoxicosis or thyroid storm.

The presence of hyperthyroidism is a marker for increased risk for the development of trophoblastic gestational neoplasia. Due to the absence in the reporting of thyroid symptoms it was not possible to determine the significance of the decreased TSH levels in the index study and was thus not evaluated further.

### Evaluation of the Beta-hCG surveillance period

#### Persistence

The risk of persistent trophoblastic disease differs between PHM's and CHM's. The incidence of persistent disease in the index study was found to be 19.7% for CHM's and 20% for PHM's (table 7). These values are much higher than the reported incidences in other studies, 15% for CHM's and 0.5% for PHM's <sup>[28,44,45]</sup>. The reasons for this difference in the incidences is largely based on the biased nature of patients referred to Tygerberg Hospital and have already been mentioned.

Wolfberg et al concluded that the risk of persistent trophoblastic neoplasia after Beta-hCG values have fallen to less than 5 mIU/mL was very small and may even approach zero<sup>[28]</sup>.

Another study by Wolfberg et al concluded that women with PHM with serum Beta-hCG levels that spontaneously declined to undetectable levels after evacuation were at exceedingly low risk of developing persistence<sup>[37]</sup>.

Feltmate et al and Batorfi et al re-evaluated the length of the follow-up period after molar pregnancies. None of the 150 patients in Batorfi's study and none of the 400 patients in Feltmate's report who achieved at least one undetectable serum HCG level had any evidence of persistent trophoblastic disease<sup>[38,39]</sup>.

In the index study, 65 patients had at least one Beta-hCG level less than 5 mIU/ml during the first 6 months after evacuation, and only 3 (4.6%) of those developed persistent disease. This is in keeping with previously reported data.

### Remission

Remission is diagnosed when a patient achieves three consecutive undetectable Beta-hCG levels during the surveillance period.

In the index study, 23 patients from each group went into remission. Three (13%) patients from the CHM group and 1 (4.3%) from the PHM group went into spontaneous remission after 6 months of surveillance (table 9). The majority of both groups went into remission before 6 months had elapsed after their primary treatment. These patients required no chemotherapy at any stage during their surveillance period, proving the validity of the current molar surveillance protocol.

Kerkmeijer et al reported that among 265 patients with spontaneous normalization, only 1 developed persistent disease<sup>[31]</sup>.

Patients who became pregnant during the 6-month follow-up interval (n=6) were considered to be in remission if they had evidence of a normal pregnancy. No postpartum Beta-hCG evaluation was performed after the subsequent pregnancy as recommended by the FIGO oncology committee<sup>[20]</sup>.

Currently, uncomplicated molar pregnancies that enter remission in less than 6 months of surveillance are not required to follow up any further. The data from the index study supports this finding.

### Compliance

The surveillance period refers to the time period after the primary evacuation when Beta-hCG levels are evaluated (table 7).

The method of surveillance of molar pregnancies after primary evacuation of the uterus is standardized according to the recommendations by the FIGO Oncology Committee <sup>[20]</sup> as described in the introduction.

In the index study, the Beta-hCG level used to determine the presence of remission was a value of less than 5 mIU/ml. This value is internationally accepted as the upper level of an undetectable reading, despite the current assay used being more capable of detecting lower levels.

The method of surveillance at Tygerberg Hospital is the same for all types of molar pregnancies. Once persistence is diagnosed, patients are managed according to the International Federation of Gynecology and Obstetrics (2000) scoring system for gestational trophoblastic neoplasia, by prognostic factors (table 9). Those that obtain a score of 0 to 6 (low risk) are eligible for monotherapy and those 7 or greater (high risk) show a high risk for resistance to monotherapy.

After primary treatment and discharge from the hospital, patients are given a follow-up date in one week at the Gynaecology Oncology unit where the Beta-hCG surveillance is commenced. These results are recorded and evaluated by a senior nurse. If the value is on the decline, the patient is given another follow-up date for the next week. This continues until 3 consecutive undetectable levels are reached. If the level is reaching a plateau or rising, the patient is presented to the gynaecologic oncologist for evaluation.

The generally used protocol worldwide for Beta-hCG surveillance, which is followed by Tygerberg Hospital is the following:

In cases of CHM's, it is recommended to check serum Beta-hCG levels weekly until undetectable for three consecutive weeks then monthly until undetectable for six consecutive months.

For patients with PHM's the monthly Beta-hCG checking is recommended only until undetectable for three consecutive months if serum Beta-hCG becomes negative within 7 weeks after curettage. Otherwise the same protocol is used as for patients with CHM's <sup>[34]</sup>.

Numerous studies found patient compliance to the protracted period of Beta-hCG surveillance to be poor. Only 16% of patients completed the entire period of Beta-hCG monitoring in the study from the Netherlands <sup>[23]</sup>. Other authors reported non-compliance in 49.5% and 40% of their patients due to either failure of follow up before undetectable levels were reached or missing data in their respective study populations <sup>[29,39]</sup>. Compliance in this study was also very poor with only 36% complying with the surveillance protocol.

Numerous patients failed to follow up for further Beta-hCG testing during the surveillance period and had to be contacted telephonically to ascertain whether any complications had developed. This contact was performed much later, sometimes a few years later, when the data was evaluated for this study in an attempt to improve the quality of the data.

Patients were telephonically asked the following questions in an attempt to establish remission:

1. Were there any episodes of abnormal vaginal bleeding during the subsequent months?
2. Was admission to another institution required for gynaecological reasons?
3. Had the patient fallen pregnant during the surveillance period?
4. Had further evacuations been required?

5. Was any further or other treatment for the molar pregnancy provided by any other healthcare facilities?

If all these questions were answered in the negative, it was accepted that the patient had entered remission and that no persistence had occurred. Although this was not the ideal method for determining persistence, it was the only plausible option available in order to collect information on molar pregnancies treated in the sample group.

#### Evaluation of potential Beta-hCG cut-off values

The cut-off values at specific time intervals were attained with the use of Receiver-Operator Characteristic (ROC) curves. If the diagnostic test is a continuous variable, as in the case of a measurement of Beta-hCG concentration in blood, then a ROC curve permits selection of a diagnostic threshold that can be used to predict adverse outcomes. By calculating the area under the ROC curve and comparing it with the area under the non-diagnostic line (the diagonal line running from the bottom left to the top right) one can determine if the test is better at predicting the outcome than chance alone.

The time periods used were week 4, week 6, month 2 and month 3. The choice for the use of these intervals was based on the premise that a dramatic shortening of the surveillance period could be attained should these values prove significant.

There were certain constraints to the evaluation of these time intervals, primarily due to the lack of compliance by the patients to their follow up visits. A large majority of the patients missed at least one visit during the first 6 months of follow up, but managed to attend the clinic later. With this in mind, the decision was made to impute no more than one data point within these four data points. For example, if a patient managed to attend on week 4 and month 2 and month 3, then the value of the Beta-hCG at week 4 was imputed into the data point for week 6. The value of the data imputed was always the same as the value immediately prior to the missed data point, so that an effective over-estimation of that point was made and in so doing, erring on the side of caution. If more patients had been

available for study and more data available, the cut-off points would have been much more accurate, offering higher sensitivities and specificities at each interval.

The data point with the best predictive value for evaluation of a potential cut-off was that of Week 6. The highest numbers of patients were evaluated at this interval (N=85). The sensitivity and specificity of this cut-off value was 0.89 and 0.88 respectively. The area under the curve was 0.9, and the recommended cut-off value was a Beta-hCG of 148 mIU/ml. The sensitivity of this cut-off point implies that 89% of our patients that developed persistence were detected by the presence of a Beta-hCG value greater than 148 mIU/ml, implying that 11% of the patients who developed persistence would not have been picked up had the surveillance period been terminated. However, 88% of patients that would not develop persistent disease would be correctly identified by a Beta-hCG value of less than 148 mIU/ml. This evaluation suggests that 12% of patients with a Beta-hCG value of less than 148 mIU/ml could develop persistent disease. Larger studies are needed to determine more accurate cut-offs that would hopefully have more clinically acceptable sensitivity and specificity levels.

It is important to note that a shortened surveillance could enable women to attempt a subsequent pregnancy sooner and for socio-economic reason limit the visits for Beta-hCG testing, but could result in late development of neoplasia with increased morbidity and mortality. Data reported at the 2009 International Society for the Study of Trophoblastic Diseases (ISSTD) world congress of 22000 women with complete and partial hydatidiform moles in the UK suggest that either form can occasionally develop post-mole neoplasia after the Beta-hCG has returned to normal; however, the risk of missed gestational trophoblastic neoplasia can be reduced from one in 800 women to one in 1400 by following present UK guidelines as mentioned above<sup>[30]</sup>.

### Recommendations

There are major pitfalls in the management of molar pregnancies in developing countries, with the majority of the effort being placed on the role of tertiary institutions, and a smaller

role on those smaller rural/district hospitals. However, the majority of the population does not have access to these larger facilities and rely solely on their local clinics for management and surveillance of this condition that has the potential for severe maternal morbidity and mortality. This emphasises the need for nurse training programs for detection of suspicious Beta-hCG results and appropriate referral.

Failure in accurate diagnosis of molar pregnancies, particularly PHM's (which are known to occur simultaneously with a normal pregnancy), remains a global problem. The costs involved in requesting histological confirmation of all adverse first trimester events is not affordable or feasible even in the most wealthy of countries. A possible solution to this dilemma could be the measurement of maternal Beta-hCG three to four weeks after a miscarriage has been diagnosed and treated, and if this result has not fallen as expected, the assumption of a molar pregnancy could be made and appropriate surveillance instituted. This method of surveillance could be tailored to that group of patients that fall into an ambiguous category and could be less stringent. This method of management would also require an initial measurement of Beta-hCG at presentation, which is not routinely performed. The management of ectopic pregnancies remains unchanged, but a more rigorous attempt at confirming a normal tubal pregnancy with histology should be emphasized.

A reasonable recommendation to improve the way molars are managed would be to institute a national registry where all molar pregnancies could be documented for further epidemiological analysis and evaluation of treatment practices. The institution of such a registry could be made simpler by forming sub-registries affiliated with each tertiary institution that would be responsible for their own drainage area. This is a very important step in the improvement of our management of molar pregnancies and would be the first step in achieving better standards of care. The United Kingdom instituted their own molar registry in 1973 as an example, and has instituted changes to their surveillance protocol based on over 30 years of patient data.



Regional guidelines with regards to the surveillance period are already in place, but this study has demonstrated the inconsistency in the record keeping for this period and will hopefully be the driving force behind instituting changes in order to better manage these conditions, particularly the benign forms of the disease.

Some highlighted recommendations follow:

- The institution of a standardised data sheet ('molar passport') for these patients, in triplicate or duplicate (one to be kept in the patients' file, one for a registry file in the gynaecology clinic and possibly a third card for the patient to keep as documentation should they follow up at other clinics) would aid in the evaluation of potential recurrence or persistence. Digitilisation of patient data would be ideal.
- Sufficient contact details should be made available to those monitoring the patients for follow up and the patients that miss an appointment should be contacted so as to improve compliance and evaluation of the surveillance period. When patients can not be reached, certified letters that describe the malignant potential of molar pregnancy and the importance of follow-up should be sent to the last known address, or social workers could be enrolled to assist in locating the patient and ascertaining the reason for non-compliance.
- The possibility of making the serum Beta-hCG surveillance tests free of charge, to take into account the socio-economic toll this protracted surveillance period takes.
- Nursing and medical education programs which assist in the counseling of these patients, in an attempt to improve understanding of the disease and thus compliance.
- The formulation of an information booklet that can be given to the newly diagnosed patient with all the relevant details on the surveillance procedure and the reason for its necessity.

- The forwarding of all patient details and the surveillance outcomes from peripheral hospitals to a centralized regional registry, namely the tertiary institution responsible for that drainage area.

It seems more appropriate for these, as yet, uncomplicated patients to be followed up at regional centres and local clinics where state-funded healthcare is offered until such time as persistence or recurrence is diagnosed, whereby they can appropriately be referred to a tertiary centre capable of managing the complication. All these cases could be recorded by the clinic and consultation with specialists would be available when necessary and all details are sent to the tertiary facility for registration in the molar registry.

### **Conclusion**

The management of molar pregnancies at our institution and in our drainage area thus far has been exemplary. However with the recent data published and some confirmation from this study, improvement of patient compliance, education and primarily medical treatment and surveillance is necessary. The data in this study showing the potential for limiting the surveillance period must be viewed in context, based on the small sample size and the poor compliance to follow-up. The authors feel that a sensitivity of 0.89 and specificity of 0.88 is insufficient and feel it would be prudent to wait for more robust data before such changes are made. More research, in the form of a multi-centred prospective cohort study, is needed before the surveillance period can safely be shortened without impacting on maternal morbidity. The development of a central registry will be pivotal in allowing for the acquisition of the data required to make these changes.

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**Illustrations****Table 1: Distinction between complete and partial moles**

<b>Feature</b>	<b>Complete mole</b>	<b>Partial mole</b>
Karyotype	Diploid: 46,XX (<15% 46,XY)	Triploid: 69,XXX/Y, (rarely 69,XYY)
Embryonic/foetal tissue	Typically absent (may be present in few cases)	Present
Villi	Diffusely hydropic	Hydropic villi with marked scalloping mixed with normal appearing chorionic villi and fetal tissue; hydropic changes are focal and less prominent than in complete mole
Trophoblastic proliferation	Hyperplastic	Less trophoblastic hyperplasia than in complete mole; trophoblastic stromal inclusions can be seen
Trophoblastic atypia	Often present	Infrequent
Immunocytochemistry	hCG, rare PLAP	hCG, PLAP, p57
Uterine size	Often large for dates	Often small for dates
Theca lutein cysts	Present in <= 25%	Rare
Malignant sequelae	Occur in up to one-third	Occur in less than 5 percent

**Table 2: Demographic Details**

Age
Parity
Gravidity
Age at Menarche
Age at First Pregnancy
Nicotine Use
Method of Primary Intervention
Contraception Use

Table 3: Comparison of PHM and CHM

<b>Variables</b>	<b>Type of Molar Pregnancy</b>	<b>Minimum</b>	<b>Maximum</b>	<b>Mean</b>	<b>Standard deviation</b>	<b>P-value</b>
<b>Age</b>	CHM	13	23	26.0	9.5	0.633
	PHM	13	49	26.4	8.3	
<b>Gravidity</b>	CHM	1	12	2.1	1.9	0.094
	PHM	1	7	2.4	1.6	
<b>Parity</b>	CHM	0.0	11	0.9	1.8	0.099
	PHM	0.0	6	1.2	1.6	
<b>Menarche</b>	CHM	11	16	13.62	1.310	0.404
	PHM	11	18	13.84	1.503	
<b>Age at First Pregnancy</b>	CHM	13	42	20.58	4.49	0.445
	PHM	13	29	18.97	3.12	
<b>TSH</b>	CHM	0.010	113	3.6	17.1	0.116
	PHM	0.010	5.0	0.8	1.2	
<b>Initial Beta-hCG</b>	CHM	1366	5407920	472715.6	817681	0.855
	PHM	2080	3467000	625496.2	900520.0	

Table 4: Comparison of Persistence compared to Age

	<b>Age &lt; 35 years</b>	<b>Age &gt;= 35 years</b>	<b>P-value</b>
<b>No Persistence</b>	79 (83.2%)	17 (68%)	0.057
<b>Persistence</b>	16 (16.8%)	8 (32%)	
<b>Total</b>	95	25	



Table 5: Nonparametric comparisons of Descriptive variables between Persistent and Non-persistent Molar pregnancies

<b>Variable</b>	<b>P-value</b>
<b>Age</b>	0.150
<b>Parity</b>	0.185
<b>Gravidity</b>	0.135
<b>Initial Beta-hCG</b>	0.717

Table 6: Beta-hCG Follow-up in patients with Complete and PHM's

<b>Histology</b>	<b>CHM</b>	<b>PHM</b>	<b>Unknown</b>
<b>Persistence Present</b>	13 (19.7%)	10 (20%)	1 (25%)
<b>No chemotherapy required, despite lack of remission diagnosis</b>	53 (80.3%)	40 (80%)	3 (75%)
<b>Lost to Follow-up &lt; 6 months after evacuation</b>	44 (66.6%)	25 (50%)	1 (25%)
<b>Did not follow up but had at least 1 undetectable Beta-hCG level</b>	14 (21%)	17 (34%)	3 (75%)
<b>Did not follow up and did not reach undetectable Beta-hCG levels</b>	49 (74.2%)	30 (60%)	2 (50%)
<b>Fell Pregnant during follow-up period, before remission</b>	3 (4.5%)	3 (6%)	0
<b>Missed at least 1 visit during first 6 months after evacuation</b>	57 (86.3%)	47 (94%)	4 (100%)
<b>Total (n=120)</b>	<b>66 (55%)</b>	<b>50 (42%)</b>	<b>4 (3%)</b>

**Table 7: Receiver Operator Characteristic Curves to Differentiate Beta-hCG levels**

	<b>Number of Cases</b>	<b>AUC</b>	<b>Sensitivity</b>	<b>Specificity</b>	<b>Cut-off Beta-hCG Value</b>
<b>Week 1</b>	77	0.76	0.69	0.79	6309
<b>Week 2</b>	68	0.76	0.67	0.86	1813
<b>Week 3</b>	69	0.78	0.92	0.67	174
<b>Week 4</b>	83	0.85	0.94	0.73	148
<b>Week 6</b>	85	0.9	0.89	0.88	148
<b>Month 2</b>	86	0.84	0.82	0.87	43
<b>Month 3</b>	76	0.72	0.64	0.8	11
<b>Month 4</b>	72	0.71	0.67	0.7	2

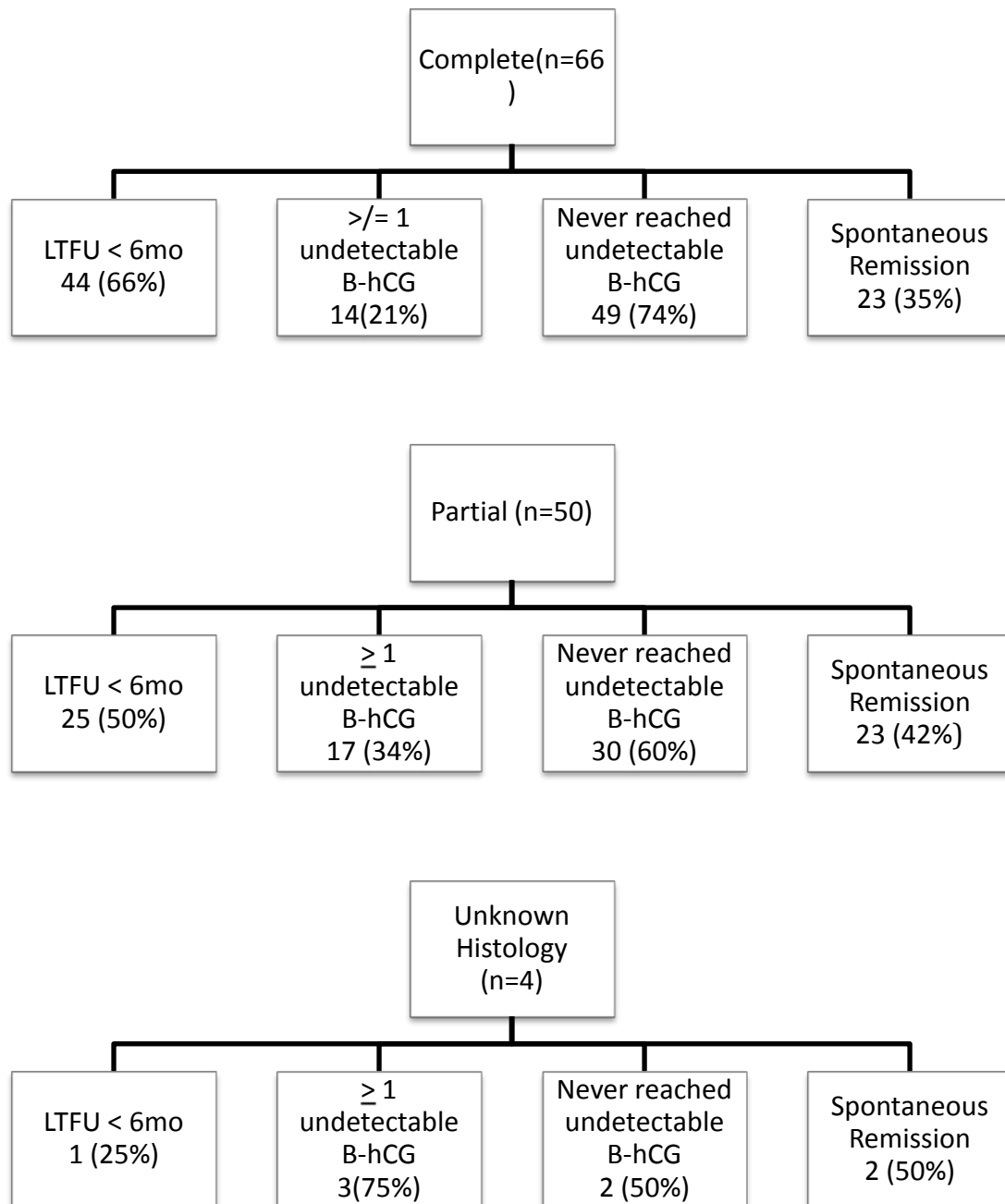
**Table 8: Remission time intervals of molar pregnancies**

<b>Remission diagnosis</b>	<b>CHM</b>	<b>PHM</b>
<b>&lt; 4 months</b>	7 (30.4%)	9 (39.1%)
<b>4-6 months</b>	13 (56.6%)	13 (56.6%)
<b>&gt; 6 months</b>	3 (13%)	1 (4.3%)
<b>Totals</b>	23	23

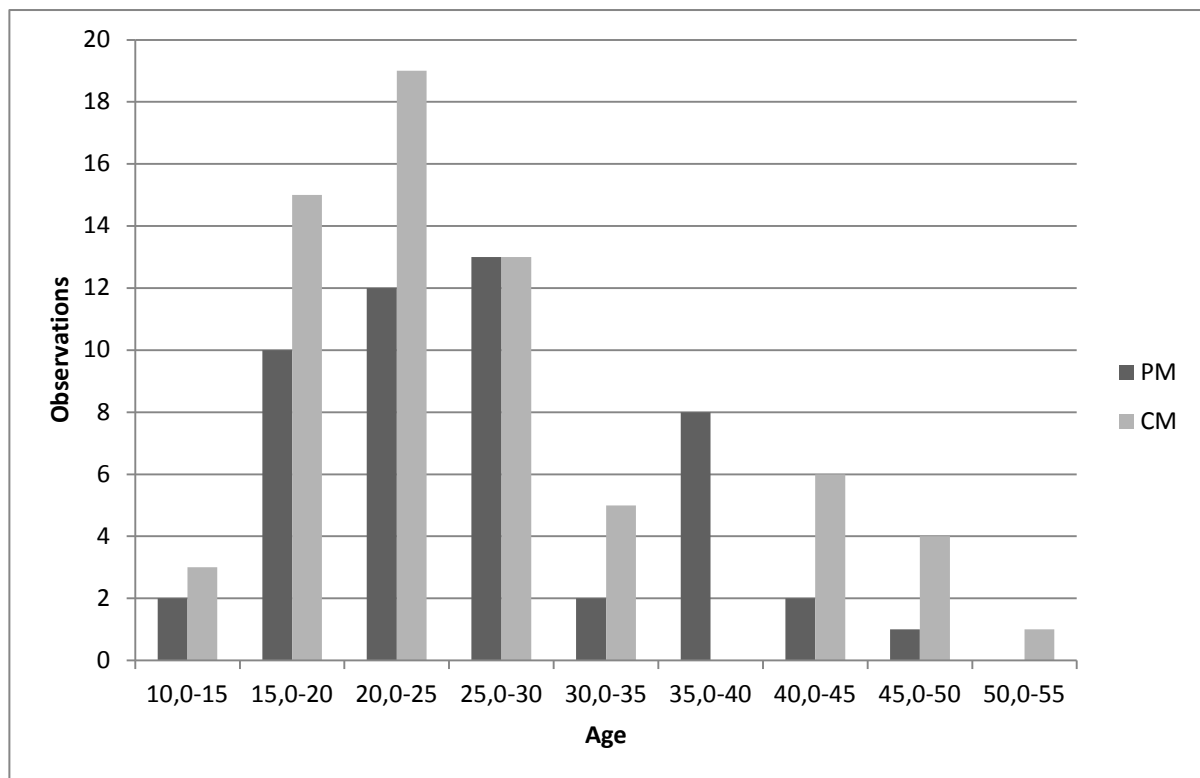
Table 9: FIGO (2000) scoring system for gestational trophoblastic neoplasia, by prognostic factor

	0	1	2	4
<b>Age</b>	< 40	≥ 40		
<b>Antecedent Pregnancy</b>	Mole	Abortion	Term	
<b>Interval to Chemotherapy</b>	< 4 months	4-6 months	7-12 months	≥ 12 months
<b>Beta-hCG (IU/l)</b>	< 10 <sup>3</sup>	10 <sup>3</sup> - < 10 <sup>4</sup>	10 <sup>4</sup> - 10 <sup>5</sup>	> 10 <sup>5</sup>
<b>Number of Metastases</b>	0	1 - 4	5 - 8	> 8
<b>Site of Metastases</b>	Lung	Spleen, kidney	GIT	Brain, liver
<b>Largest tumour mass diameter (CHM)</b>		3 -5 CHM	> 5 CHM	
<b>Previous Chemotherapy</b>			Monotherapy	Combined Chemotherapy

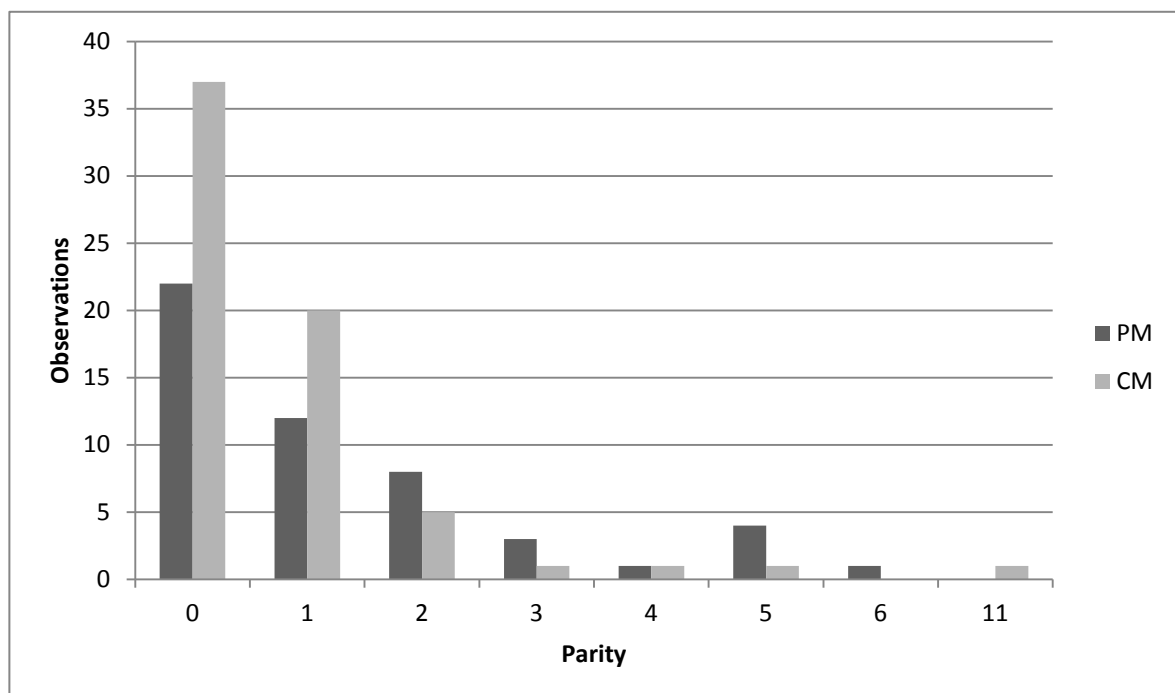
Figure 1: Follow Up among 120 patients with Molar Pregnancies



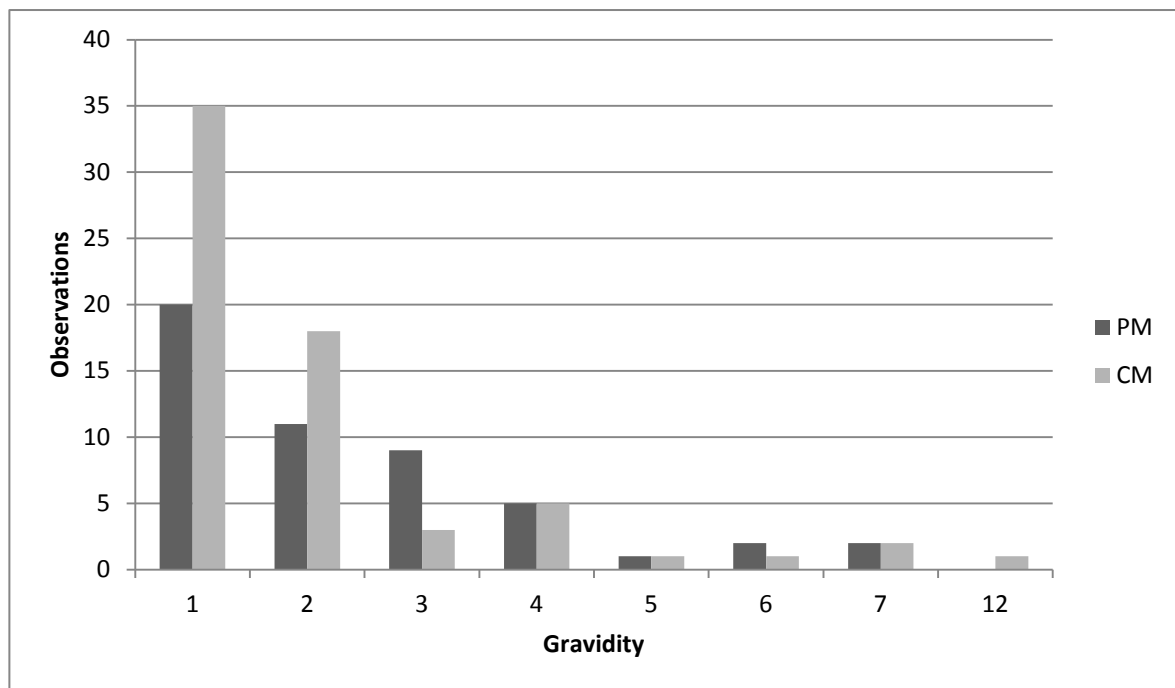
**Figure 2: Histogram of Maternal Age Distribution**



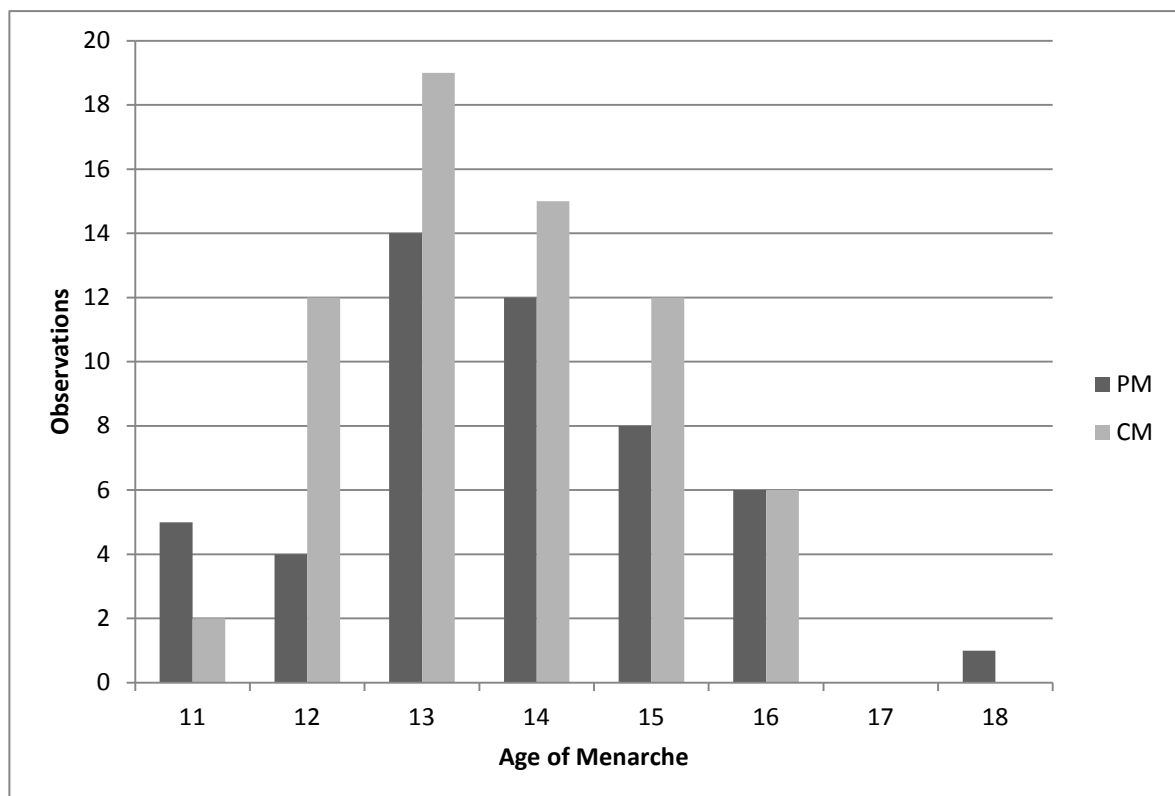
**Figure 3: Histogram of Parity Distribution**



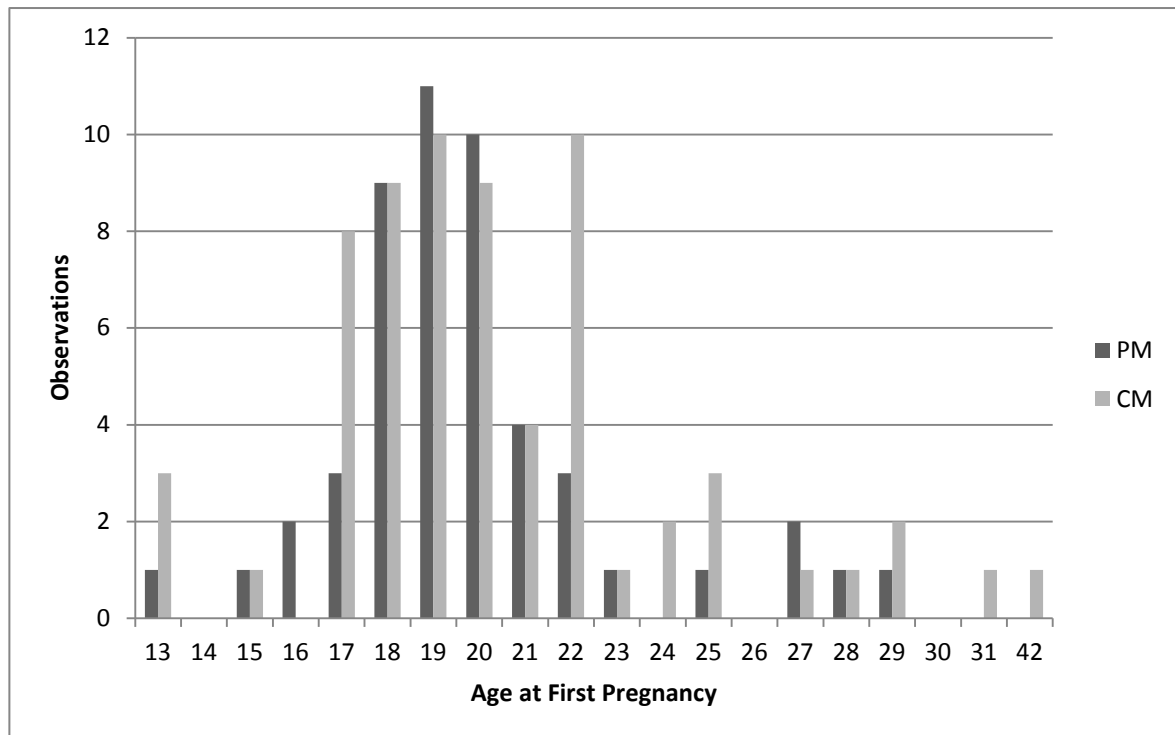
**Figure 4: Histogram of Gravidity Distribution**



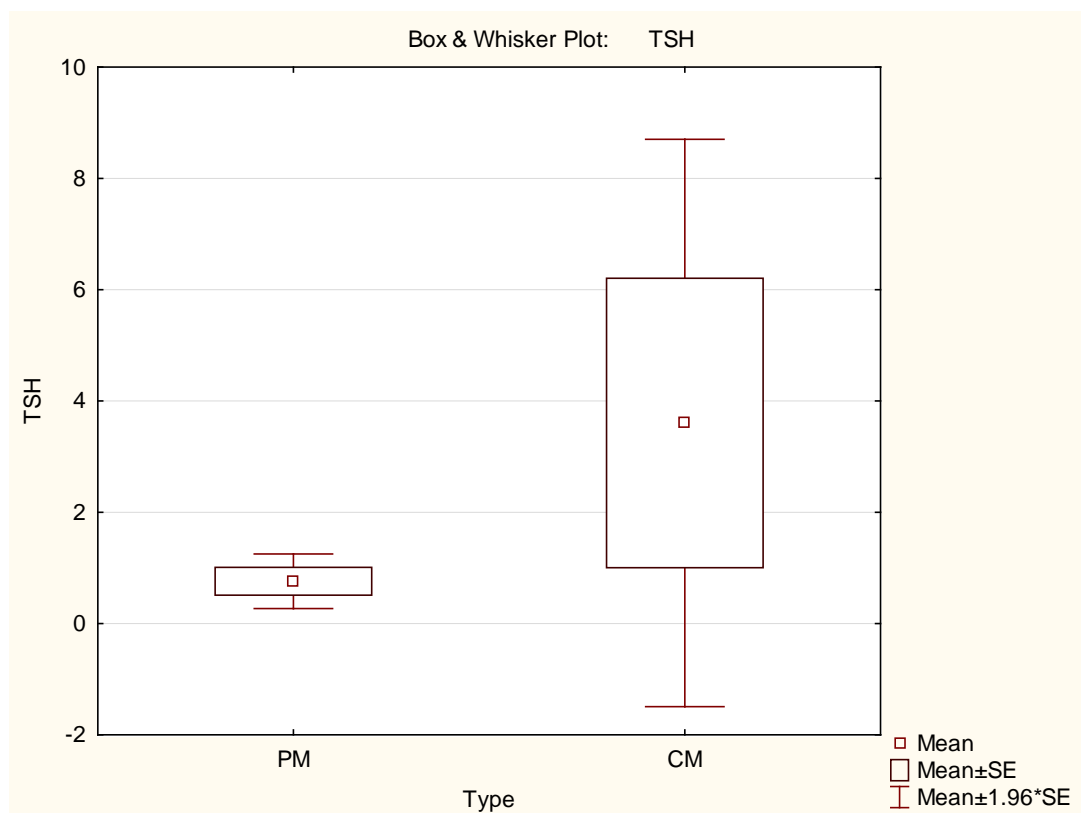
**Figure 5: Histogram of Menarche Distribution**



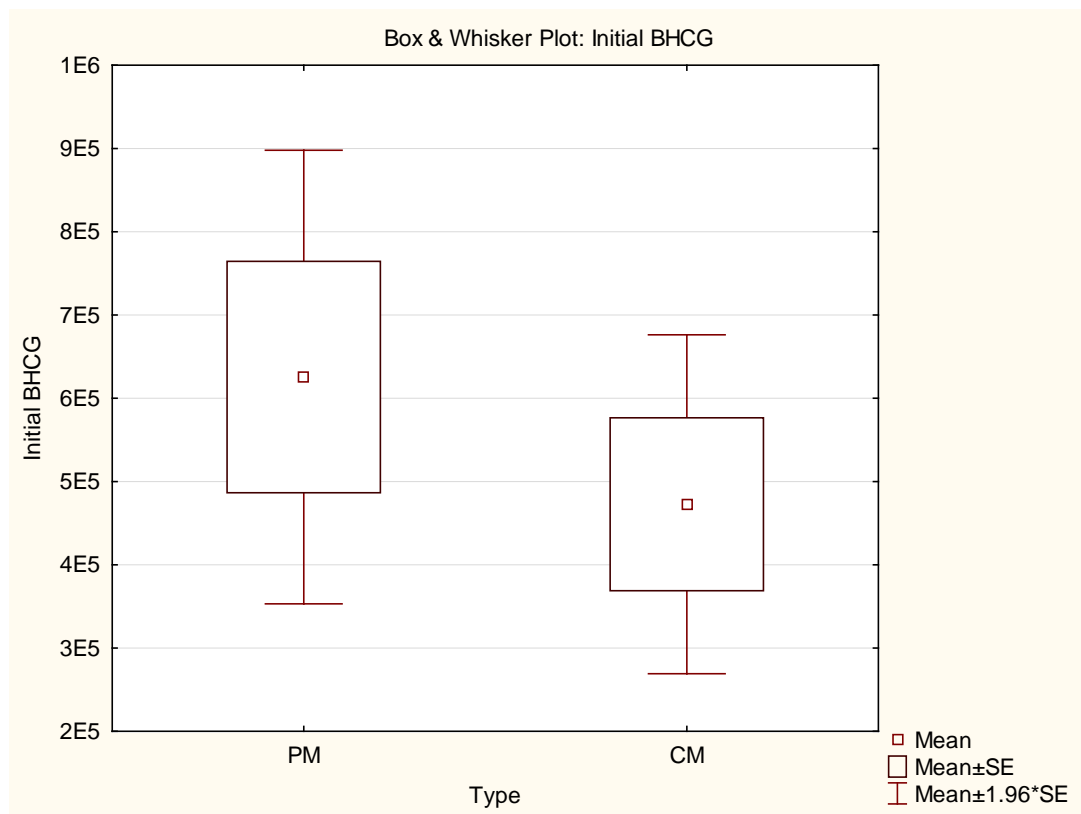
**Figure 6: Histogram of Age at First Pregnancy Distribution**



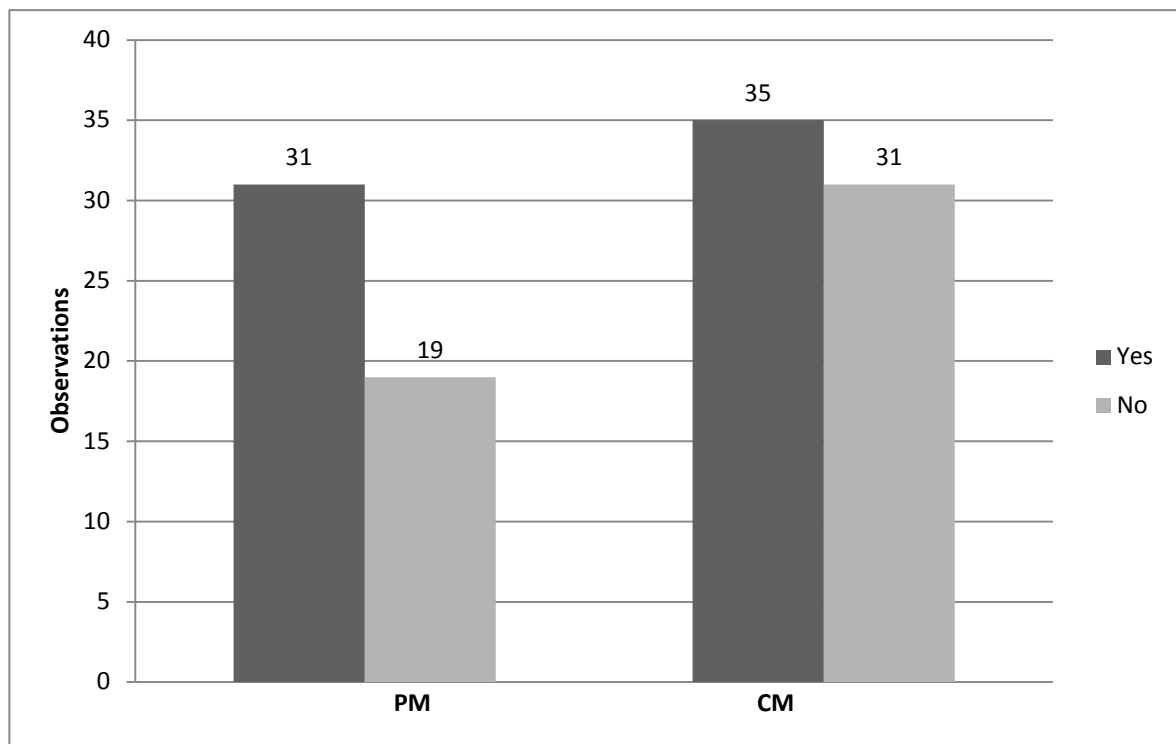
**Figure 7: Box and Whisker Plot of TSH Levels**



**Figure 8: Box and Whisker Plot of Initial Beta-hCG Levels**

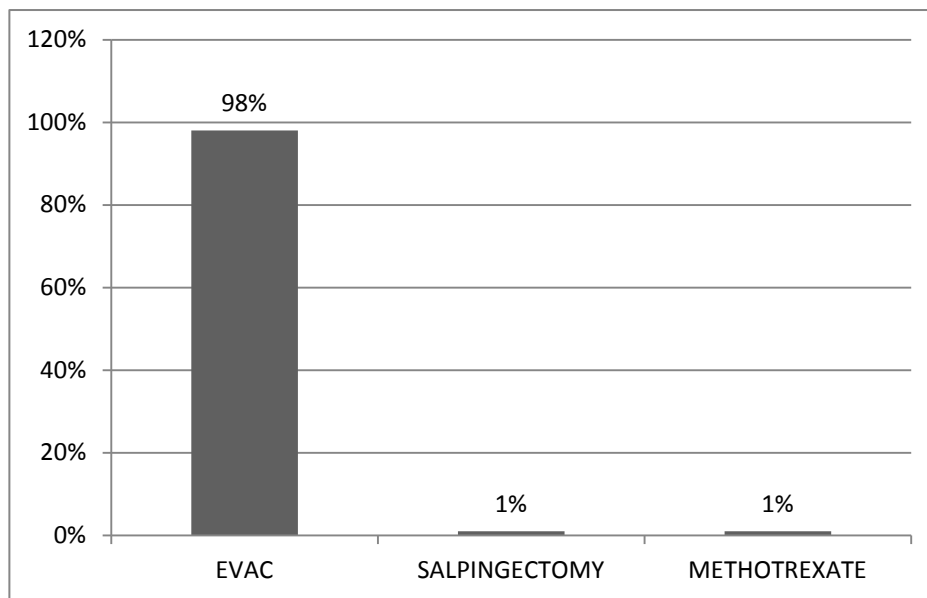


**Figure 9: Histogram of Smoking Practices**





**Figure 10: Histogram of Treatment Modalities**



**Figure 11: Receiver Operator Characteristic Curve for Beta-hCG Values at Week 4**

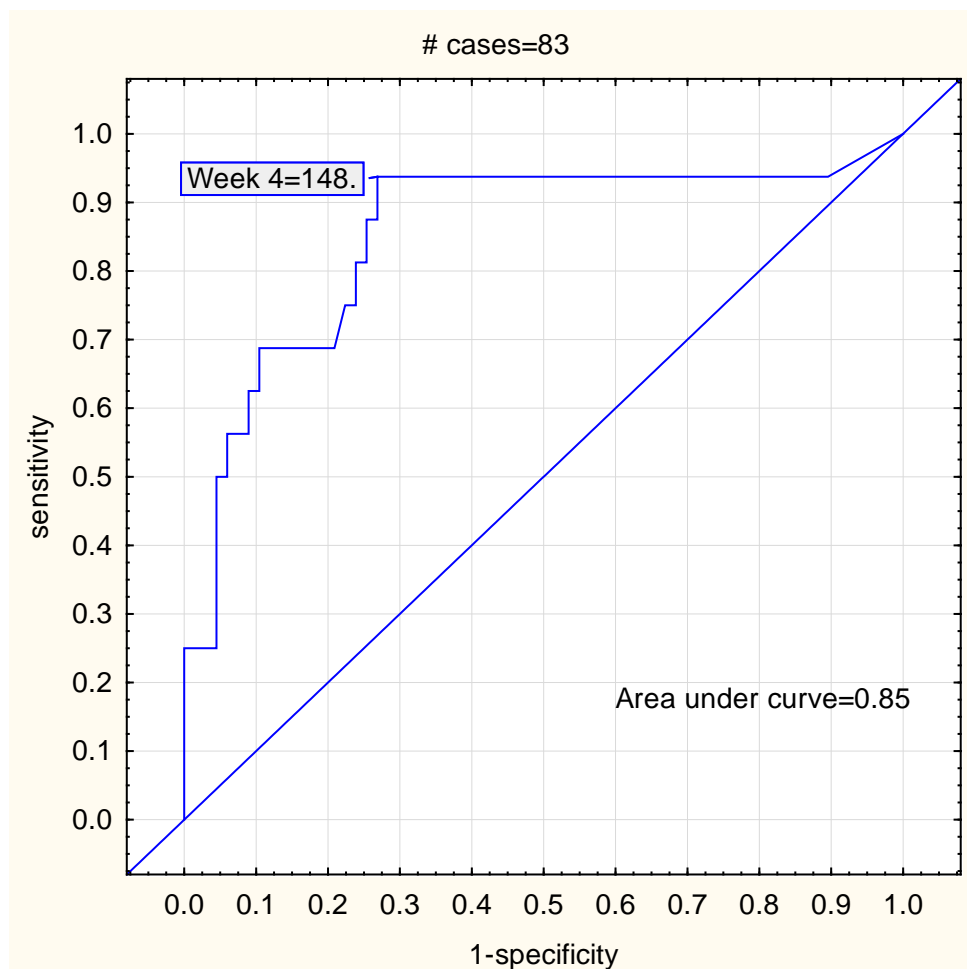


Figure 12: Receiver Operator Characteristic Curve for Beta-hCG Values at Week 6

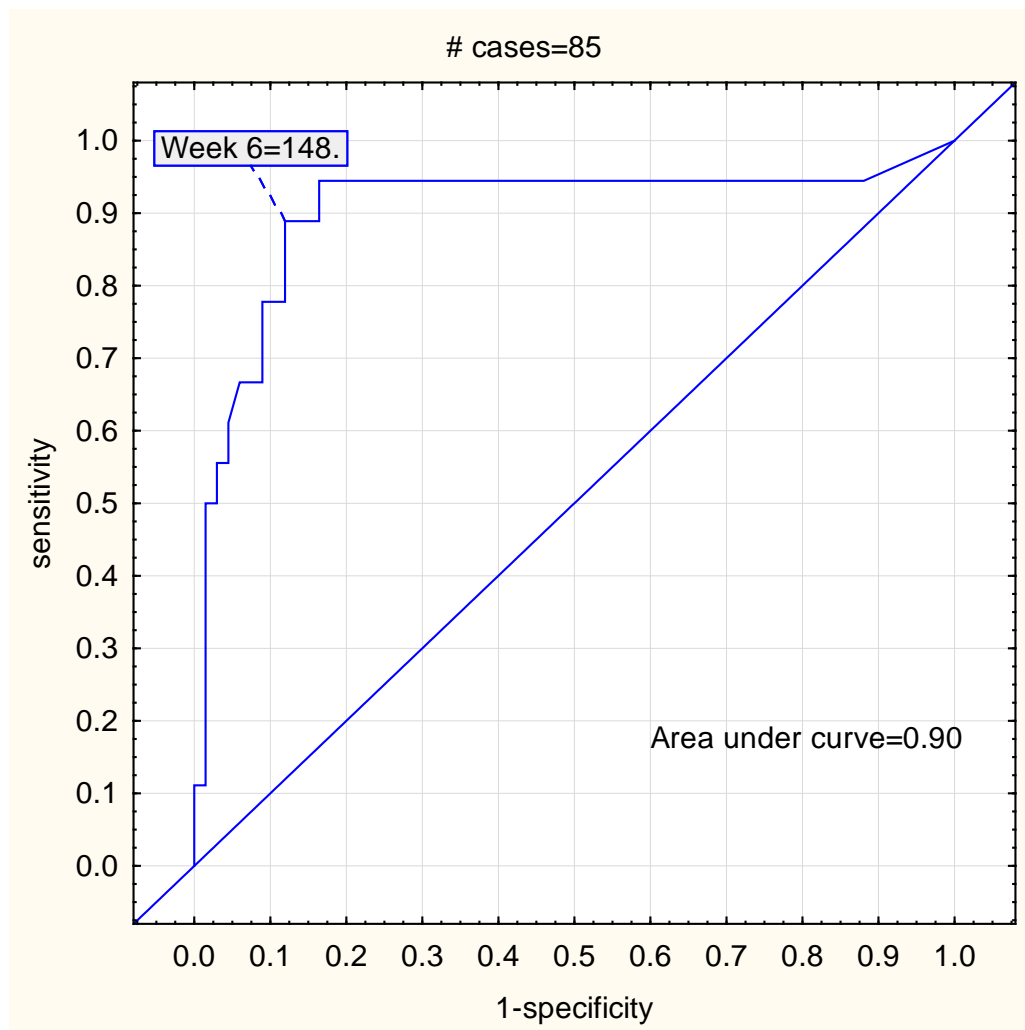


Figure 13: Receiver Operator Characteristic Curve for Beta-hCG Values at Month 2

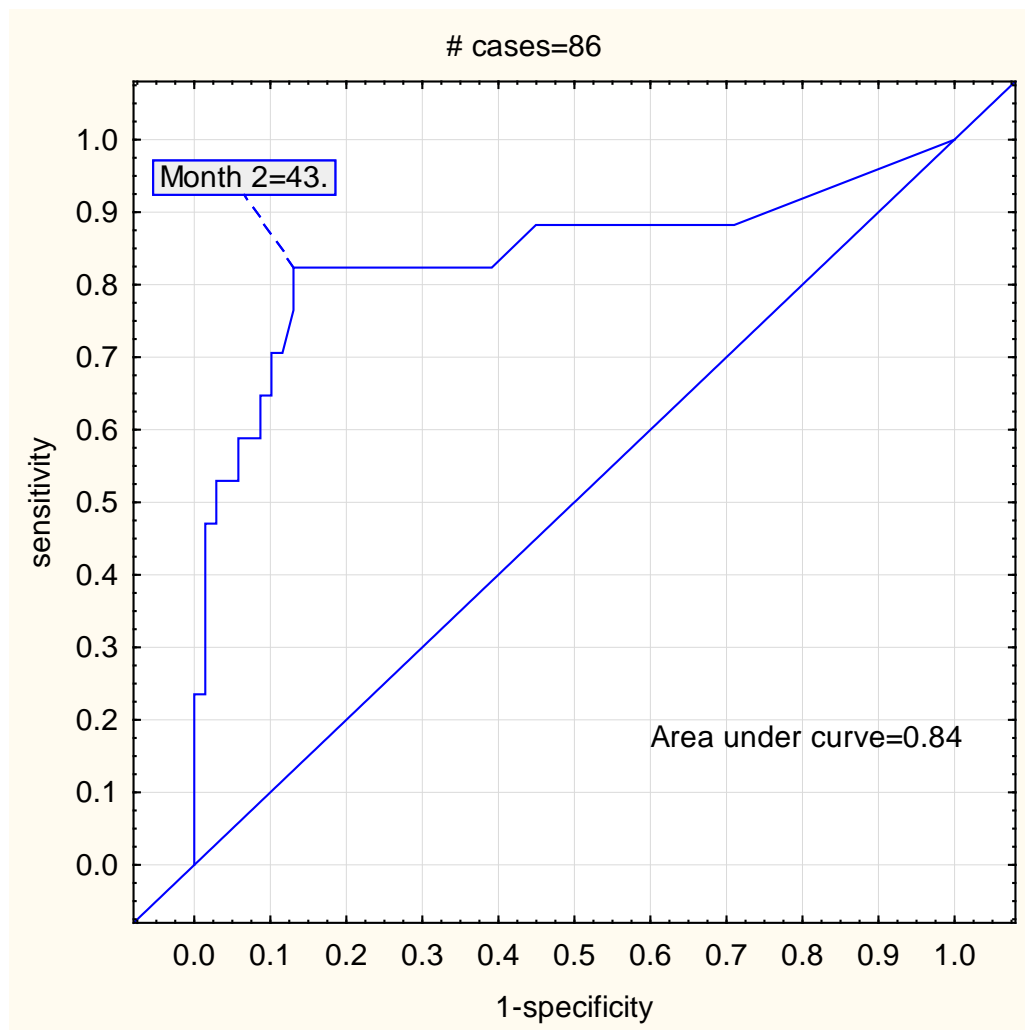
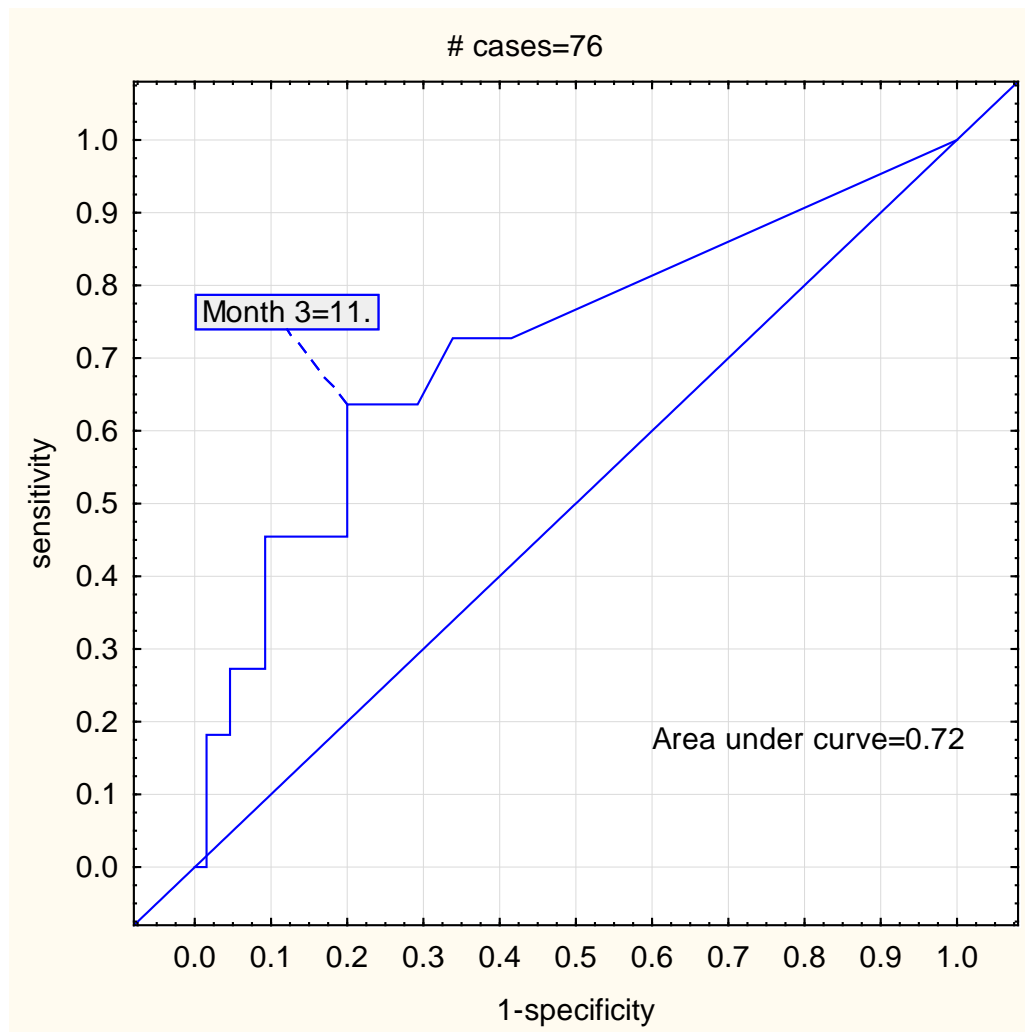


Figure 14: Receiver Operator Characteristic Curve for Beta-hCG Values at Month 3



Addendum A: Data Sheet

**DATA SHEET**

Case Number	_____			
Histology	_____			
Age	_____	Parity	_____	Gravidity _____
Nationality	_____			
TSH:	_____			Menarche _____
T4:	_____			First Pregnancy _____
Beta-hCG:	_____			Smoker (Y/N) _____
<b>Follow Up Beta-hCG</b>				
Week 1	_____			
Week 2	_____			
Week 3	_____			
Month 1	_____			
Week 5	_____			
Week 6	_____			
Week 7	_____			
Month 2	_____			
Week 9	_____			
Week 10	_____			
Week 11	_____			
Month 3	_____			
Month 4	_____			
Month 5	_____			
Month 6	_____			
Month 9	_____			
Year 1	_____			
Month 18	_____			
Year 2	_____			
Persistence (Y/N)	_____			
Recurrence (Y/N)	_____			
Lost to Follow-up (Y/N)	_____			
Telephonically contacted (Y/N)	_____			